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(54) Mouse-human chimaeric immunoglobulin heavy chain, and chimaeric DNA encoding it.

(57) A mouse-human chimaeric immunoglobulin heavy chain comprising (a) the amino acid sequence of a mouse immunoglobulin heavy chain variable region and (b) the amino acid sequence of a human immunoglobulin heavy chain constant region and reacting specifically with human common acute lymphocytic leukemia antigen and a chimaeric DNA fragment which encodes the amino acid sequence of the above mouse-human chimaeric immunoglobulin heavy chain.

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What is claimed is:

1. A mouse-human chimaeric immunoglobulin heavy chain comprising (a) the amino acid sequence of a mouse immunoglobulin heavy chain variable region and (b) the amino acid sequence of a human immunoglobulin heavy chain constant region and reacting specifically with human common acute lymphocytic leukemia antigen.

2. The chimaeric immunoglobulin heavy chain of claim 1 wherein the amino acid sequence of the variable region is derived from a mouse immunoglobulin heavy chain which reacts specificaly with human common acute lymphocytic leukemia antigen.

3. The chimaeric immunoglobulin heavy chain of claim 1 wherein the amino acid sequence of the constant region is derived from the heavy chain of a human immunoglobulin G.

4. The chimaeric immunoglobulin heavy chain of claim 3 wherein the human immunoglobulin G is human immunoglobulin G_1.

5. The chimaeric immunoglobulin heavy chain of claim 1 wherein the variable region contains a V-segment having the following amino acid sequence

Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val
Gln Pro Gly Gly Ser Arg Lys Leu Ser Cys Ala Ala
Ser Gly Phe Thr Phe Ser Ser Phe Gly Met His Trp
Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val
Ala Tyr Ile Ser Gly Gly Ser Tyr Thr Ile Tyr Tyr
Ala Asp Thr Val Lys Gly Arg Phe Thr Ile Ser Arg
Asp Asn Pro Lys Asn Thr Leu Phe Leu Gln Met Thr
Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys
Ala Ser Ser Tyr Gly Asn Phe Trp Tyr Phe Asp Val
Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser

wherein the various abbreviations stand for the following amino acids:

Gly: glycine
Ala: alanine
Val: valine

Leu: leucine
Ile: isoleucine
Ser: serine
Asp: aspartic acid
Lys: lysine
Arg: arginine
His: histidine
Phe: phenylalanine
Tyr: tyrosine
Thr: threonine
Cys: cysteine
Met: methionine
Glu: glutamic acid
Trp: tryptophan
Pro: proline
Asn: asparagine
Gln: glutamine.

6. The chimaeric immunoglobulin heavy cvhain of claim 5 wherein the variable region has the following amino acid sequence

Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val
Gln Pro Gly Gly Ser Arg Lys Leu Ser Cys Ala Ala
Ser Gly Phe Thr Phe Ser Ser Phe Gly Met His Trp
Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val
Ala Tyr Ile Ser Gly Gly Ser Tyr Thr Ile Tyr Tyr
Ala Asp Thr Val Lys Gly Arg Phe Thr Ile Ser Arg
Asp Asn Pro Lys Asn Thr Leu Phe Leu Gln Met Thr
Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys
Ala Ser Ser Tyr Gly Asn Phe Trp Tyr Phe Asp Val
Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser Ser
Tyr Gly Asn Phe Trp Tyr Phe Asp Val Trp Gly Ala
Gly Thr Thr Val Thr Val Ser Ser

wherein the abbreviations for the amino acids are as shown in claim 5.

7. The chimaeric immunoglobulin heavy chain of claim 1 wherein the constant region has the following amino acid sequence

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
Leu Gly Gys Leu Val Lys Asp Tyr Phe Pro Glu Pro
Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Gys Asn
Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
Thr Leu MET Ile Ser Arg Thr Pro Glu Val Thr Cys
Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn
Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
MET Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
Gln Gln Gly Asn Val Phe Ser Cys Ser Val MET His

wherein the abbreviations for the amino acids are as shown in claim 5.

8. The chimaeric immunoglobulin heavy chain of claim 1 which has the following amino acid sequence

Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val
Gln Pro Gly Gly Ser Arg Lys Leu Ser Cys Ala Ala
Ser Gly Phe Thr Phe Ser Ser Phe Gly Met His Trp
Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val
Ala Tyr Ile Ser Gly Gly Ser Tyr Thr Ile Tyr Tyr
Ala Asp Thr Val Lys Gly Arg Phe Thr Ile Ser Arg

Asp Asn Pro Lys Asn Thr Leu Phe Leu Gln Met Thr
Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys
Ala Ser Ser Tyr Gly Asn Phe Trp Tyr Phe Asp Val
Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser Ser
Tyr Gly Asn Phe Trp Tyr Phe Asp Val Trp Gly Ala
Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys
Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro
Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu MET Ile
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
Thr Leu Pro Pro Ser Arg Glu Glu MET Thr Lys Asn
Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
Val Phe Ser Cys Ser Val MET His Glu Ala Leu His
Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
Gly Lys

wherein the abbreviations for the amino acids are as shown in claim 5.

9. A chimaeric DNA fragment which encodes the amino acid sequence of the mouse-human chimaeric immunoglobulin heavy chain of claim 1.

10. The chimaeric DNA fragment of claim 9 which contains a variable region V-segment DNA sequence represented by the following

GAT GTG CAG CTG GTG GAG TCT GGG GGA GGC TTA GTG
CAG CCT GGA GGG TCC CGG AAA CTC TCC TGT GCA GCC
TCT GGA TTC ACT TTC AGT AGC TTT GGA ATG CAC TGG
GTT CGT CAG GCT CCA GAG AAG GGG CTG GAG TGG GTC
GCA TAT ATT AGT GGT GGC AGT TAT ACC ATC TAC TAT
GCA GAC ACA GTG AAG GGC CGA TTC ACC ATC TCC AGA
GAC AAT CCC AAG AAC ACC CTG TTC CTA CAA ATG ACC
AGT CTA AGG TCT GAG GAC ACG GCC ATG TAT TAC TGT
GCA AGT TCC TAT GGT AAC TTC TGG TAC TTC GAT GTC
TGG GGC GCA GGG ACC ACG GTC ACC GTC TCC TCA

wherein A represents deoxyadenosine-5'-phosphate, C represents deoxycytidine-5'-phosphate, G represents deoxyquinosine-5'-phosphate, and T represents deoxythymidine-5'-phosphate,

and a DNA sequence complementary thereto.

11. The DNA sequence of the chimaeric DNA fragment of claim 10 which contains a variable region DNA sequence represented by the following

GAT GTG CAG CTG GTG GAG TCT GGG GGA GGC TTA GTG
CAG CCT GGA GGG TCC CGG AAA CTC TCC TGT GCA GCC
TCT GGA TTC ACT TTC AGT AGC TTT GGA ATG CAC TGG
GTT CGT CAG GCT CCA GAG AAG GGG CTG GAG TGG GTC
GCA TAT ATT AGT GGT GGC AGT TAT ACC ATC TAC TAT
GCA GAC ACA GTG AAG GGC CGA TTC ACC ATC TCC AGA
GAC AAT CCC AAG AAC ACC CTG TTC CTA CAA ATG ACC
AGT CTA AGG TCT GAG GAC ACG GCC ATG TAT TAC TGT
GCA AGT TCC TAT GGT AAC TTC TGG TAC TTC GAT GTC
TGG GGC GCA GGG ACC ACG GTC ACC GTC TCC TCA TCC
TAT GGT AAC TTC TGG TAC TTC GAT GTC TGG GGC GCA
GGG ACC ACG GTC ACC GTC TCC TCA

Wherein A, C, G and T are as defined in claim 10, and a DNA sequence complementary thereto.

12. The chimaeric DNA fragment of claim 9 which contains a human immunoglobulin heavy chain constant region DNA fragment comprising

(1) a C_H1 segment which contains DNA sequence represented by the following

GCC TCC ACC AAG GGC CCA TCG GTC TTC CCC CTG GCA
CCC TCC TCC AAG AGC ACC TCT GGG GGC ACA GCG GCC
CTG GGC TGC CTG GTC AAG GAC TAC TTC CCC GAA CCG
GTG ACG GTG TCG TGG AAC TCA GGC GCC CTG ACC AGC
GGC GTG CAC ACC TTC CCG GCT GTC CTA CAG TCC TCA
GGA CTC TAC TCC CTC AGC AGC GTG GTG ACC GTG CCC
TCC AGC AGC TTG GGC ACC CAG ACC TAC ATC TGC AAC
GTG AAT CAC AAG CCC AGC AAC ACC AAG GTG GAC AAG
AAA GTT

(2) an h segment which contains a DNA sequence represented by the following

GAG CCC AAA TCT TGT GAC AAA ACT CAC ACA TGC CCA
CCG TGC CCA

(3) a C_H2 segment which contains a DNA sequence represented by the following

GCA CCT GAA CTC CTG GGG GGA CCG TCA GTC TTC CTC
TTC CCC CCA AAA CCC AAG GAC ACC CTC ATG ATC TCC
CGG ACC CCT GAG GTC ACA TGC GTG GTG GTG GAC GTG
AGC CAC GAA GAC CCT GAG GTC AAG TTC AAC TGG TAC
GTG GAC GGC GTG GAG GTG CAT AAT GCC AAG ACA AAG
CCG CGG GAG GAG CAG TAC AAC AGC ACG TAC CGG GTG
GTC AGC GTC CTC ACC GTC CTG CAC CAG GAC TGG CTG
AAT GGC AAG GAG TAC AAG TGC AAG GTC TCC AAC AAA
GCC CTC CCA GCC CCC ATC GAG AAA ACC ATC TCC AAA
GCC AAA

and (4) a C_H3 segment which contains a DNA sequence represented by the following

GGG CAG CCC CGA GAA CCA CAG GTG TAC ACC CTG CCC
CCA TCC CGG GAG GAG ATG ACC AAG AAC CAG GTC AGC

CTG ACC TGC CTG GTC AAA GGC TTC TAT CCC AGC GAC
ATC GCC GTG GAG TGG GAG AGC AAT GGG CAG CCG GAG
AAC AAC TAC AAG ACC ACG CCT CCC GTG CTG GAC TCC
GAC GGC TCC TTC TTC CTC TAT AGC AAG CTC ACC GTG
GAC AAG AGC AGG TGG CAG CAG GGG AAC GTC TTC TCA
TGC TCC GTG ATG CAT GAG GCT CTG CAC AAC CAC TAC
ACG CAG AAG AGC CTC TCC CTG TCC CCG GGT AAA

wherein A, C, G and T are as defined in claim 10, and a DNA sequence complementary to said constant region DNA sequences.

13. The chimaeric DNA fragment of claim 9 comprising a DNA fragment encoding the amino acid sequence of the variable region and a DNA fragment encoding the amino acid sequence of the constant region joined to each other through a DNA sequence containing at least a human enhancer.

14. The chimaeric DNA fragment of claim 13 wherein the human enhancer contains a DNA sequence represented by the following

TTG GCG AGC TGG AAG CAG ATG ATG AAT TAG AGT CAA
GAT GGC TGC ATG GGG GTC TCC GGC ACC CAC AGC AGG
TGG CAG GAA GCA GGT CAC CGC GAG AGT CTA TTT TAG
GAA GCA AAA AAA CAC AAT TGG TAA ATT TAT CAC TTC
TGG TTG TGA AGA GGT GGT TTT GCC AGG CCC AGA TCT
GAA AGT GCT CTA CTG AGC AAA ACA ACA CTT GGA CAA
TTT GCG TTT CTA AAA TAA GGC GAG GCT GAC CGA AAT
CGA AAG GCT TTT TTT AAC TAT CTG CAA TTT CAT TTC
CAA TCT TAG CTT ATC AAC TGC TAG TTG G

wherein A, C, G and T are as defined in claim 10, and a DNA sequence complementary thereto.

15. Recombinant pSV2gpt plasmid harboring the chimaeric DNA fragment of claim 9.

16. Mouse myeloma J558LK or NS-1 cells into which the chimaeric DNA fragment of claim 9 has been introduced by using the recombinant plasmid of claim 15.